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COMPLETE SPECIFICATION

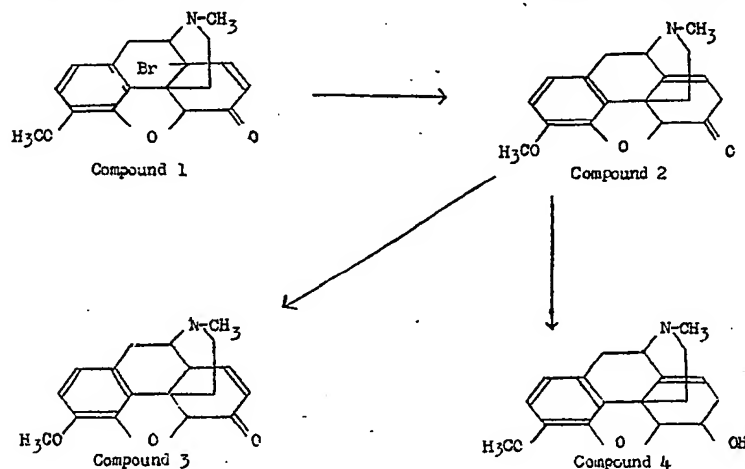
Morphine Alkaloids

5 We, MERCK & Co., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

10 This invention relates to the preparation of codeinone and neopine; and is more particularly concerned with the preparation of

codeinone and neopine from 14-bromo-
codeinone, and with neopine, an intermediate
compound thus obtained. 15

In accordance with this invention 14-bromocodeinone (Compound 1) is treated with hydrogen in the presence of a hydrogenation catalyst and a neutral solvent to produce neopinone (Compound 2), a new compound. The neopinone is converted to codeinone (Compound 3) by heating, or is reacted with an alkali-metal borohydride to form neopine (Compound 4). These reactions may be 25 chemically represented as follows:



30 The 14-bromocodeinone is treated with hydrogen in the presence of a hydrogenation catalyst and a neutral solvent to produce neopinone. The hydrogenation catalyst is desirably a noble metal. The preferred catalysts are metals of the platinum group, palladium supported on a carrier, for example charcoal or barium sulphate, being particularly suitable, but other noble-metal catalysts such as oxides of metals of the platinum group may also be used. Other carriers, for example calcium carbonate, are also suitable. 35

The hydrogenation catalyst is preferably used 40 in a range of one-quarter to ten per cent by weight based on the weight of the 14-bromocodeinone, although additional catalyst can be used if desired.

The reaction may be carried out by using 45 hydrogen at sub-atmospheric, atmospheric or super-atmospheric pressure, but is preferably carried out at slightly over atmospheric pressure. The temperature of the reaction may be varied to control the rate of reaction, but a 50 temperature of 0° to 75°C. is preferred,

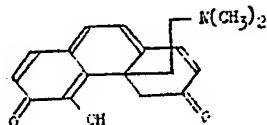
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approximately room temperature being the most desirable because it reduces the amount of equipment required. The neutral solvent should include an alcohol containing from one to eight carbon atoms in the molecule, the lower alkanols being the most desirable. It is preferred to have at least five per cent by weight of the alcohol present. The reaction proceeds quite rapidly until one mole of hydrogen is absorbed.

The reaction is preferably carried out by dissolving or suspending the 14-bromo-codeinone in a non-polar diluent or unreactive solvent, such as benzene, toluene, xylene, ethylene dichloride, chloroform, ethyl acetate or acetone. The hydrogenation catalyst is then added to the solution and the solution is agitated while subjecting it to the action of hydrogen. When the conversion is complete, the product, the hydrobromic-acid addition salt, is converted to the free compound by the addition of a base, such as potassium carbonate, and separated from the reaction mixture by suitable means, such as by filtering the reaction mixtures to remove the catalyst, concentrating the reaction mixture, and crystallizing the neopinone by the addition of a non-solvent, such as ethyl acetate.

This hydrogenolysis is surprising, in view of the fact that the double bond already conjugated with the carbonyl group in 14-bromo-codeinone moves to a position away from the carbonyl, in which position it loses the stabilization of resonance.

Neopinone is converted to the acid addition salts by reacting with an acid, such as hydrochloric acid, hydrobromic acid, citric acid, tartaric acid or sulphuric acid. The acid addition products possess different solubility characteristics. Neopinone readily forms a methiodide at room temperature which can be converted to an intense violet dye by the addition of aqueous alcohol. The dye forms equally well under nitrogen but its formation is accelerated by the addition of a weak base. The dye is purified by chromatography on Florisil yielding a crystalline product in the form of black needles having a melting point of 183°C. This dye has the formula:



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Neopinone when crystallized from a solution containing substantial proportion of chloroform, preferably 50% ethyl acetate and 50% chloroform, forms a crystal form having a melting point *ca.* 92°C. (with decomposition). The solvate is fairly stable in air at 25°C. but rapidly loses chloroform when heated at 100°C. The calculated per cent of

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chloroform for a one to one ratio adduct is 28.5%. Since the solvate is far less soluble in the crystallization medium than the unsolvated form and the accompanying impurities in the neopine preparations do not form such solvates, the use of this effect is considerably helpful in the isolation and purification of neopinone.

The neopinone is heated to form codeinone. This reaction is carried out by merely heating the neopinone, preferably in a solvent, and the rate of reaction is dependent upon the rate of heating. It is desirable, however, to obtain optimum yield, to carry out the reaction by refluxing neopinone with activated carbon in a suitable solvent. The rate of reaction will vary depending on the particular components of the reaction mixture; as an example, when the solvent is ethyl acetate and the neopinone is refluxed with an equal amount of activated carbon, the reaction is complete in two to four hours. The heating may be carried out at the melting point of neopinone, at which temperature the reaction is rapid, although it is more desirable to carry out the reaction at a lower temperature in order to maintain better control over the reaction. The course of reaction may be conveniently followed by infrared absorption or by measuring optical rotation. Any non-reactive solvent or diluent may be used, such as an organic ester, benzene, chloroform, alcohol or ether. The most desirable solvent is one in which the product is insoluble. The product is recovered by filtering the reaction mixture and concentrating under reduced pressure which crystallizes the codeinone.

The neopinone is reacted with an alkali-metal borohydride to produce neopine. The reaction is preferably carried out in a non-reactive solvent or diluent, such as water, a lower aliphatic alcohol or aqueous mixtures of lower aliphatic alcohols. By "alkali-metal borohydride" is meant any of those boron compounds having an alkali metal associated with a group consisting of a boron atom and at least one and up to four reactive hydrogen atoms. When there are fewer than four hydrogen atoms, the group containing the boron atom may contain one to three univalent atoms other than hydrogen or one to three univalent radicals, which atoms or radicals are relatively inert and non-reactive with respect to the reducing action characteristic of the hydrogen atoms of these compounds, or a combination of such atoms other than hydrogen and radicals so long as at least one hydrogen atom is present and so long as the total number of atoms including hydrogen and radicals is four.

The reaction is most conveniently effected by dissolving or suspending the neopinone in a lower aliphatic alcohol, and adding the alkali-metal borohydride to the alcoholic solution or suspension either as a solid or in the

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form of a suspension in a lower aliphatic alcohol. The resulting reaction mixture is then permitted to stand at room temperature for sufficient time to insure completion of the reduction. The neopine compound can be readily recovered from the reaction mixture by conventional methods known in the art. Thus, the reduction product can be recovered by direct crystallization from the reaction mixture. Alternatively, the product may be recovered by diluting the reaction mixture with water, adding alkali and extracting the alcohol with a suitable water-immiscible solvent, such as chloroform. This reaction is surprising since it might be expected to yield the *iso* compound.

The neopinone is not only useful as an intermediate for producing neopine and codeinone from 14-bromocodeinone, but it also possesses antitussive activity and may prove useful as an antitussive agent.

An alternative method for the conversion of neopine to codeinone consists in reaction with a weak aqueous acid such as aqueous potassium bisulphate. The reaction is ordinarily carried out at room temperature although higher or lower temperatures will be satisfactory. At room temperature the conversion is allowed to take place over an extended period of time, such as one to three weeks, although the reaction time may be increased or decreased depending upon the temperature.

The following examples are given for purposes of illustration.

EXAMPLE 1

A solution of 18.8 grams (0.05 mol.) of 14-bromocodeinone in a mixture of 200 cc. of benzene and 70 cc. of methanol containing 4.0 grams of 10% palladium on charcoal was shaken with hydrogen at 25°C. The absorption of hydrogen was rapid until one molar equivalent had been taken up, when the absorption practically ceased. The catalyst was removed by filtration and the clear, nearly colourless, solution was shaken with a cold solution of 7.0 grams of potassium carbonate in 200 cc. of water. The benzene solution of the free base was washed twice with cold, 1% sodium sulphate solution, and then concentrated below 40°C. under reduced pressure. After the addition of ethyl acetate and ether the neopinone was obtained in the form of nearly colourless fine needles which melted sharply between 118°C. and 130°C. depending on the rate of heating $[\alpha]_D^{23} = -12.1^\circ$ (Chloroform, $C=0.873$).

EXAMPLE 2

Two grams of neopinone in 10 milliliters of methanol were reacted with 0.6 gram of sodium borohydride suspended in 12 milliliters of methanol. The mixture was allowed to stand for one and one-half hours, concentrated to one-half the original volume and diluted with 10 cc. of ten per cent sodium

hydroxide. The solution was heated momentarily to boiling, diluted with water, extracted with chloroform and concentrated to yield neopine.

EXAMPLE 3

A 58.0 gram sample of 14-bromocodeinone was dissolved in a mixture of 200 cc. of chloroform and 100 cc. of benzene. The solution was filtered to remove a trace of insoluble matter. Methanol (20 cc.) and 5.0 grams of ten per cent palladium charcoal were added and the mixture hydrogenated at 50 pounds per square inch initial pressure. After several hours the absorption practically ceased at a pressure drop corresponding to 97% of theory for one molar equivalent of hydrogen. The catalyst was filtered off, and the clear brown solution of neopinone hydrobromide was shaken with a solution of 21.3 grams of potassium carbonate (0.154 mole) in 200 cc. of ice water, dried over 30 grams of anhydrous sodium sulphate and evaporated under reduced pressure below 40°C. The solid crystalline residue was pumped dry in a good vacuum, then recrystallized from 100 cc. of warm (40°C.) ethyl acetate. Thorough cooling (-20°C.) was employed to obtain the maximum separation of product. The combined yield over several crops was 37.0 grams (80%) of colourless to pinkish needles of neopinone, melting point ca. 125°C.

EXAMPLE 4

Neopinone (2.0 grams) was refluxed in 20 cc. of ethyl acetate with 2.0 grams of Darco G-60 charcoal for 2 hours under slight nitrogen pressure. ("Darco" is a registered Trade Mark). The mixture was cooled and filtered, and the charcoal cake was washed with another 20 cc. of hot ethyl acetate. The filtrates were combined and evaporated under reduced pressure until the codeinone began to crystallize; the product was left overnight in the refrigerator to complete the crystallization.

EXAMPLE 5

Neopinone (10.0 grams) was refluxed under slight nitrogen pressure with 10 grams of Darco G-60 charcoal in 80 cc. of ethyl acetate for 5 hours. The charcoal was removed and washed with 100 cc. of hot ethyl acetate in small portions. The combined filtrates were evaporated under reduced pressure to a volume of about 30 cc. and then cooled to 0°C. The product codeinone crystallized upon continued cooling.

What we claim is:—

1. The process that comprises treating 14-bromocodeinone with hydrogen in the presence of a hydrogenation catalyst and a neutral solvent to produce neopinone.
2. A process according to Claim 1, in which the catalyst is a noble metal.
3. A process according to Claim 2, in which the reaction is carried out in the presence of a supported palladium hydrogenation catalyst.

- tion catalyst and a lower aliphatic alcohol.
4. The process that comprises heating neopinone to form codeinone.
- 5 5. A process according to Claim 4, in which the neopinone is admixed with activated charcoal.
6. A process according to Claim 4 or 5, carried out in a medium comprising ethyl acetate.
- 10 7. The process which comprises reacting neopinone with an alkali-metal borohydride as hereinbefore defined to form neopine.
8. A process according to any one of Claims 4—7 in which the neopinone has been prepared by a process according to any one of Claims 1—3.
- 15 9. Neopinone.
10. Acid addition salts of neopinone.
11. Neopinone hydrobromide.
12. A solvate complex consisting of chloroform and neopinone.
- 20 13. A process according to Claim 1, when carried out substantially as described in Example 1 or 3.
14. A process according to Claim 4, when carried out substantially as described in Example 4 or 5.
- 25 15. A process according to Claim 7, when carried out substantially as described in Example 2.
16. Neopinone when prepared by a process according to any one of Claims 1—3 and 13 or its obvious chemical equivalent.
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